UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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October 27, 1999

MEMORANDUM

SUBJECT: Phosmet - Report of the Cancer Assessment Review Committee

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

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The Cancer Assessment Review Committee met on September 1, 1999 to evaluate the carcinogenic potential of Phosmet. Attached please find the Final Cancer Assessment Document.

cc: K. Baetcke
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# *CANCER ASSESSMENT DOCUMENT*

EVALUATION OF THE CARCINOGENIC POTENTIAL OF

## ***PHOSMET*** *(THIRD REVIEW)*

FINAL REPORT

27-OCTOBER-1999

CANCER ASSESSMENT REVIEW COMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

DATA PRESENTATION: Linda Taylor, Toxicologist

DOCUMENT PREPARATION: Sanjivani Diwan, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the assessment unless otherwise stated).

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William Burnam

Marion Copley

Kerry Dearfield

Vicki Dellarco

Yiannakis Ioannou

Nancy McCarroll

Esther Rinde

Jess Rowland

Joycelyn Stewart

Clark Swentzel

Linda Taylor

NON-COMMITTEE MEMBERS IN ATTENDANCE (Signature indicates concurrence with the pathology report and statistical analysis of data, respectively)

Lori Brunsman, Statistical Analysis

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## EXECUTIVE SUMMARY

On September 1, 1999, the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Programs met to reconsider the carcinogenicity classification of Phosmet under the draft Agency Risk Assessment Guidelines (1996; 1999) for the human cancer risk assessment.

Previously, the Cancer Peer Review Committee (CPRC; Document No. 010998, dated May 26, 1994) classified Phosmet as a Group C- possible human carcinogen and recommended the Reference Dose (RfD) approach for quantification of human cancer risk. This decision was based on an increased incidence of liver adenomas and combined adenomas and carcinomas in male B6C3F1 mice at the high dose. The increase was statistically significant by pair-wise comparison, with a statistically significant trend, and there was an apparent early onset. Females had a significant dose-related trend for liver carcinomas and combined adenomas/carcinomas as well as for mammary gland adenocarcinomas. The majority opinion of the CPRC was that the animal evidence, using the NTP criteria, was "equivocal" for carcinogenic activity of Phosmet with studies showing a marginal increase in neoplasms in the mouse that may be chemically related. The overall consensus of the CPRC, based on the criteria contained in the Agency's Guidelines in a weight-of-the evidence determination, was that the evidence for Phosmet was "limited" and met the criteria for a Group C. There was no evidence for carcinogenicity in rats. Phosmet was determined by the CPRC to be a direct-acting mutagen *in vitro*, which did not require exogenous metabolic activation to induce the effect, and was negative in mutagenicity assays with whole animals.

At the September 1, 1999 CARC meeting, information/data previously not available to the CPRC were considered which include a revised tumor count for the mammary gland tumors observed in the high-dose female mice, recently submitted mutagenicity studies, and a published paper with results of a study comparing Phosmet and Dimethoate [structural analog] in a DNA alkylation study.

Under the Draft Guidelines for Carcinogen Risk Assessment (July, 1999), Phosmet is classified in the category **"Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential".** The CARC's decision was based on the following:

1. There was increase (both trend and pair-wise) in combined liver adenomas/carcinomas in **male** B6C3F1 mice but only trends for increase of liver adenomas/carcinomas and mammary adenocarcinomas in female B6C3F1 mice. There was no evidence of carcinogenicity in an acceptable study in Charles River rats.

2. Phosmet was **negative** in *in vivo* mutagenicity assays and **positive** in *in vitro* mutagenicity assays. The SAR data are conflicting. Phosmet is structurally related to Dimethoate which has been shown to be both carcinogenic and mutagenic. Azinphos-methyl, another organophosphate pesticide that is

considered to be more structurally similar to Phosmet, has been shown to be negative in mutagenicity and carcinogenicity studies.

Because there is low confidence that there is a potential cancer risk to humans, the Committee recommended that quantification using the tumor data is not warranted.

## I. INTRODUCTION

Previously, the Carcinogenicity Peer Review Committee (CPRC) met on November 17, 1993 and January 26, 1994 to discuss and evaluate the weight-of-the-evidence on Phosmet with regard to its carcinogenic potential. The CPRC classified Phosmet as Group C and recommended a Reference Dose (RfD) approach for the quantification of human cancer risk.

On September 1, 1999, the Cancer Assessment Review Committee (CARC) met to discuss the clarification of Phosmet under the Agency's Draft Guidelines for Carcinogen Risk Assessment [1996, 1999].

Additional data/information previously not available to the CPRC were discussed, which included new, recently submitted, mutagenicity data and a revised statistical analysis of the female mouse mammary tumor data.

## II. EVALUATION OF CARCINOGENICITY AND OTHER EVIDENCE

The tumor data are discussed in the previous CPRC document on Phosmet [HED Document No. 010998, dated March 25, 1994] and are not reiterated here.

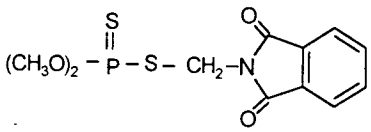
Just prior to the September 1, 1999 meeting of the Cancer Assessment Review Committee [CARC], the Registrant, Gowan, submitted several pieces of information/data for consideration by the CARC. These included an Addendum II to the mouse carcinogenicity study [MRID 40595501], which consists of documentation of a data entry that incorrectly listed one Harderian gland tumor as a mammary tumor (Taylor, 1999). The Registrant indicated that this addendum had been submitted previously but apparently had not been considered by the CPRC. In their cover letter dated August 31, 1999, Gowen states that when the corrected data are considered, "there is no significant trend for mammary tumors in the mouse." The change in the number of mammary adenocarcinomas is from 5 to 4 at the high-dose level. **However, HED's assessment (Brunsman, 1999) of the new number concludes that a significant trend is still apparent [old p=0.007; new p=0.022]. There were no other changes in the tumor data.**

The Registrant submitted three mutagenicity studies (including one from the published literature) for Committee's consideration, but these have not been formally reviewed to date [submitted by FAX on August 31, 1999]. The new studies support the previous CPRC assessment of the mutagenic potential of Phosmet, in that Phosmet displays negative evidence for genotoxicity/mutagenicity ***in vivo***. A preliminary review of the reports of these mutagenicity studies indicates that two may be acceptable (*in vivo* UDS and *in vitro* DNA alkylation assays) and the other (*in vivo* UDS assay) may be unacceptable.

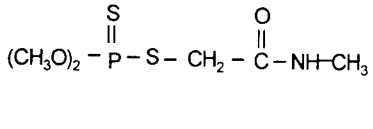
## III. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE-EVIDENCE

There were no substantive changes in tumor incidence from that considered by the CPRC. With respect to the mutagenicity data, the new acceptable studies (UDS and DNA alkylation assays) support the previous assessment of the mutagenic potential of Phosmet, in that Phosmet displays both positive [*in vitro* Ames and cell transformation assays] and negative [*in vivo* mouse micronucleus and UDS as well as *in vitro* DNA alkylation assays] evidence for genotoxicity/mutagenicity. A preliminary assessment of the new studies indicates a nongenotoxic effect.

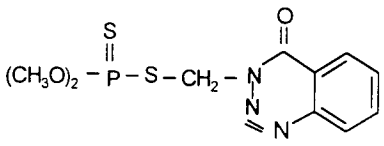
Previously, Dimethoate was the only compound listed as structurally similar to Phosmet, but Dr. Yin-Tak Woo/EPA Woo noted that Azinphos-methyl should be considered more structurally similar. The Registrant had pointed this out also in the recent submission. However, Azinphos-methyl is negative in mutagenicity and carcinogenicity studies.



Phosmet



Dimethoate



Azinphos-methyl

Also discussed was species differences in the detoxification process, but there are no data available to date for any assessment of how humans metabolize the compound or on whether Phosmet reaches the liver.

## IV. CLASSIFICATION OF CARCINOGENIC POTENTIAL

Under the Draft Guidelines for Carcinogen Risk Assessment (July, 1999), the Committee concluded that Phosmet is classified into the category "Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential" based on the following weight-of-the-evidence:

1. There was increase (both trend and pair-wise) in combined liver adenomas/carcinomas in **male** B6C3F1 mice but only trends for increase of liver adenomas/carcinomas and mammary adenocarcinomas in female B6C3F1 mice. The evidence of carcinogenicity was limited to mice, and the increase in the occurrence of tumors was marginal. There was no evidence of carcinogenicity in an acceptable study in Charles River rats.

2. Phosmet was **negative** in *in vivo* mutagenicity assays and **positive** in *in vitro* mutagenicity assays. These findings indicate that Phosmet has intrinsic mutagenic potential which is not expressed in whole animals. Phosmet is structurally related to Phosmet is structurally related to Dimethoate which has been shown to be both carcinogenic and mutagenic. Azinphos-methyl, another organophosphate pesticide that is considered to be more structurally similar to Phosmet, has been shown to be negative in mutagenicity and carcinogenicity studies.

## V. QUANTIFICATION OF CARCINOGENIC POTENTIAL

Because there is low confidence that there is a potential cancer risk to humans, the Committee recommended that quantification using the tumor data is not warranted.

## VI. BIBLIOGRAPHY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|---|---|
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| --------- | Taylor, LL. (1999). Modified data Package For Determining the Appropriate Means for Quantifying human Cancer Risk. A memorandum by Linda L Taylor, Reregistration Branch 1 to the Executive Secretary, CARC, Health Effects Division, dated August 17, 1999. |